Furukawa CT, DuHamel T, Weimer L, et al: Cognitive and behavioral findings in children taking theophylline versus cromolyn (Abstr). J Allergy Clin Immunol 1986 Jan; 77(pt 2):186

McLoughlin J, Nall M, Isaacs B, et al: The relationship of allergies and allergy treatment to school performance and student behavior. Ann Allergy 1983 Nov; 51:506-510

Rachelefsky G, Wo J, Adelson J, et al: Behavior abnormalities and poor school performance due to oral theophylline (T) usage (Abstr). J Allergy Clin Immunol 1986 Jan; 77(pt 2):145

Springer C, Goldenberg B, Ben Dov I, et al: Clinical, physiologic, and psychologic comparison of treatment by cromolyn or theophylline in childhood asthma. J Allergy Clin Immunol 1985 Jul; 76:64-69

The Management of Asthma During Pregnancy

ASTHMA is probably the most common potentially serious medical condition to complicate pregnancy. Retrospective studies suggest that maternal asthma increases the incidence of preterm births, infants with low birth weights and perinatal deaths. Although confirmatory data are lacking, the accepted working hypothesis is that adequate control of asthma during pregnancy is the most important factor in reducing this excess risk.

Optimal management of asthma during pregnancy may involve environmental control measures, immunotherapy, medication or a combination of these approaches. Decreased exposure to avoidable triggering factors (household pets, other allergens, smoking) is an obvious, but sometimes underused, therapeutic modality. Immunotherapy is considered safe during pregnancy in women who are already deriving benefit from it; conservative dosing is recommended to minimize the chance of an anaphylactic reaction. The benefit-risk ratio does not usually favor beginning immunotherapy during pregnancy.

Pharmacologic management of asthma during pregnancy is more problematic because no asthma medication can be considered proved safe during pregnancy according to the recent Food and Drug Administration (FDA) pregnancy classification. There are a number of asthma medications, however, that appear to involve less risk during pregnancy than the risk of the uncontrolled asthma that could result if they were not used. Reassuring data in humans are available for ephedrine, theophylline, cromolyn sodium, beclomethasone dipropionate and prednisone/prednisolone. In addition, terbutaline sulfate has been used extensively in the management of premature labor, although there are no reported data in humans during early pregnancy. Inhaled bronchodilators are recommended by some authors because of their topical route and, in the case of terbutaline, the favorable FDA pregnancy classification based on reassuring animal data. The optimal sympathomimetic drug of choice for the treatment of acute asthma during pregnancy (parenterally given epinephrine or terbutaline, or mechanically nebulized bronchodilators) is not uniformly agreed upon, but, as noted above, adequate control of the asthma is the most important challenge in that situation.

Although pharmacokinetic changes have been reported to occur during pregnancy, theophylline is the only asthma medication for which gestational pharmacokinetic data are available. One study of ten pregnant women with asthma suggests that the clearance of theophylline may be prolonged during later pregnancy but that the weight-corrected volume of distribution does not change during pregnancy. Thus, the recommendations for milligram-per-kilogram loading doses of theophylline do not need to be altered during pregnancy, but maintenance doses may need to be reduced. Because the data reveal significant interpatient variation in gestational theophylline pharmacokinetics, determining theophylline concentrations at least once each trimester is recommended in pregnant patients receiving theophylline regularly.

MICHAEL SCHATZ, MD
San Diego

REFERENCES

Greenberger PA, Patterson R: Management of asthma during pregnancy. N Engl J Med 1985; 312:897-902

Millstein LG: FDA's 'pregnancy categories' (Letter). N Engl J Med 1980 Sep 18; 303:706

Schatz M, Zeiger RS, Mellon M, et al: Asthma and allergic diseases during pregnancy: Management of the mother and prevention in the child, *In* Middleton E Jr, Reed CE, Ellis EF (Eds): Allergy: Principles and Practice, 2nd Ed. St Louis, CV Mosby, 1983, pp 935-986

Nonsedating Antihistamines in the Treatment of Allergic Disease

ALTHOUGH THE EFFECTS OF HISTAMINE have been known for 75 years, it was not until 1937 that Daniel Bovet was able to antagonize this mediator with the first antihistamine, compound 929F. Although he received a Nobel prize for his work, this compound was too toxic for human use. Now, more than 50 different antihistamines in six different classes are available by prescription or over the counter in the United States.

We now know that there are H_1 and H_2 histamine receptors, but we are most concerned with H_1 receptor activity in cases of allergy, whereas H_2 receptors primarily regulate gastric secretion of hydrochloric acid. The effects of classic antihistamines on H_1 receptors in the central nervous system, with resulting sedation and their anticholinergic effect on mouth dryness, limit their usefulness in many patients. The unwanted effects of sedation are due primarily to the lipid solubility of these older compounds, which allows them to cross the blood-brain barrier into the central nervous system and affect the H_1 receptors in the brain. The newer nonsedating antihistamines are often analogues or even active metabolites of classic antihistamines. Their molecular structure, however, interferes with passage into the brain. Many of the new nonsedating antihistamines are currently under clinical development, but three drugs—astemizole, mequitazine and terfenadine—are available for use in many countries.

In May 1985, terfenadine (Seldane) was approved for use in the United States as a 60-mg tablet to be administered twice a day for the treatment of seasonal allergic rhinitis. This compound has been shown to be an effective H_1 receptor antagonist for most patients with allergic rhinitis. In clinical trials, the incidence of sedation has been no greater than that reported by patients taking a placebo. Twice-a-day dosing increases patients' compliance, and the lack of central nervous system and anticholinergic side effects encourages continued use. Activity is seen in most patients after a single dose, but maximum response may not occur for three days.

Astemizole is currently available in many countries as a 10-mg tablet and should be given approval by the Food and Drug Administration for use in the United States by spring

1987. This compound has a very strong affinity for H_1 receptors and a half-life of several days, which accounts for its long duration of activity. This effect permits once-a-day dosing, but it may result in the prolonged inhibition of immediate hypersensitivity skin test reactions. The drug has been effective in treating chronic urticaria and allergic rhinitis. A somewhat slow onset of activity in some patients may be overcome by giving a loading dose of 20 to 30 mg a day for the initial one to three days of therapy.

Mequitazine is a nonsedating antihistamine that has a somewhat narrow therapeutic-to-sedation range. It, too, has a slower onset of activity than terfenadine, but it has been used successfully in Europe for controlling allergic symptoms. Recent studies indicate not only that it is an antagonist of histamine but that it also has the capacity to inhibit mediator release. There are currently no ongoing clinical trials in the United States, so its availability in this country is uncertain.

Most clinical studies with the new nonsedating antihistamines have shown them to be as effective as classic antihistamines in controlling the symptoms of allergic rhinitis. Not all patients respond, however, or respond equally. Furthermore, it appears that some patients whose symptoms are adequately controlled during periods of moderate antigen exposure derive less benefit during peak periods of antigen concentration. Some of these compounds have a longer duration of action, which has raised the question of cumulative effects with prolonged use. There is currently no evidence of this in standard patient care, but the possibility may exist in cases of drug overdose.

At least five other nonsedating antihistamines are under development in the United States. Some of these can be administered once a day, others will be available in a liquid formulation for children and some will be combined with a systemic decongestant such as pseudoephedrine.

The advent of these newer nonsedating antihistamines will offer physicians a wider choice of medication to inhibit the adverse effects of histamine in their allergic patients. Because antihistamines only block the effect of histamine, however, for some patients greater relief of symptoms awaits the development of medications that can prevent or modify the release of, or the effects of, the other mediators of the allergic response. Nevertheless, this new class of nonsedating antihistamines allows the almost 50% of all allergy patients who report sedation from classical antihistamines the opportunity to obtain relief without significant side effects.

JAMES P. KEMP, MD
ELI O. MELTZER, MD
San Diego

REFERENCES

Kemp JP, Buckley CE, Gershwin ME, et al: Multicenter, double-blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. Ann Allergy 1985 Jun; 54:502-509

Trzeciakowski JP, Levi R: Antihistamines, *In* Middleton E Jr, Reed CE, Ellis EF (Eds): Allergy: Principles and Practice, 2nd Ed. St Louis, CV Mosby, 1983, pp 575-592

Neuropeptides

THE MECHANISMS by which functionally distinct cells communicate and in the process regulate their physiologic capacities is one of the most active areas of experimentation in modern biology. Early investigations showed that neuropeptides, hormones and lymphokines mediated diverse intercellular modulatory functions in separate systems such as the central nervous, endocrine and immune systems, respectively. It is now clear, however, that bidirectional communication between each of these three systems occurs, and, in the case of neuroimmune interactions, lymphokines such as interleukin 1 and 2 may activate glial cells and astrocytes, whereas neuropeptides have now been shown to modulate immediate hypersensitivity and cell-mediated immune responses.

Neuropeptides released from peripheral sensory nerves including substance P, vasoactive intestinal peptide and somatostatin are potent mediators of smooth muscle and vascular functions. Substance P has been observed to contract intestinal smooth muscle, produce the vasodilation of systemic arterioles and increase the secretion of glycoprotein-rich fluid from human tracheal epithelium, whereas the vasoactive intestinal peptide causes intestinal smooth muscle relaxation and increased vasodilation of cutaneous microvessels. These effects may contribute to the plasma extravasation and alterations in blood flow that accompany inflammatory responses.

The modulation of immediate hypersensitivity reactions by neuropeptides is suggested by the elevated local tissue concentrations of peptides such as substance P and somatostatin detected during acute responses. In vitro studies have shown that substance P acts selectively on mast cells, but not basophils, by an IgE-independent mechanism to cause the release of histamine, leukotrienes and other mediators. In contrast, somatostatin expresses only minimal mast cell-activating activity and may modulate hypersensitivity reactions by indirect mechanisms by inhibiting the release of mediators from immunologically activated basophils.

An understanding of the mechanisms by which neuropeptides alter cell-mediated immune responses has been derived principally from in vitro experimentation. Peptides such as somatostatin and vasoactive intestinal peptide show mainly inhibitory effects on T- and B-lymphocyte activities such as proliferation and immunoglobulin synthesis, respectively. These responses are thought to be mediated by the elevation of intracellular 3′:5′-cyclic adenosine monophosphate levels in response to the neuropeptides binding to specific cell-surface receptors. In contrast, substance P has been shown to exert a stimulatory influence on T-lymphocyte proliferation and to increase the production of IgA from gut-derived lymphocytes. Experiments suggest that these substance P effects are also receptor mediated and are a result of substance P-induced activation of the phosphatidylinositol pathway in a distinct subset of lymphocytes.

The concept of the possible participation of neuropeptides in the pathogenesis of certain disease states has come largely from their chemical or immunochemical detection in tissue extracts or fluids, or by showing that locally administered neuropeptides mimic the features of hypersensitivity. Substance P has been detected in the nasal secretions of humans with allergic rhinitis and in the tissues of patients with urticaria. Its role in these conditions, however, and in other disease states where its immunopathologic role has been suggested, such as in arthritis and asthma, has yet to be conclusively determined. Progress in our understanding of how neuropeptides modulate neuronal and nonneuronal homeo-